REMARKS

Claims 9 and 11-12 were rejected under 35 U.S.C. Section 112. Applicants appreciate the suggestion of the Examiner. Claim 9 has accordingly been amended and it is believed that Claims 9 and 11-12 should be allowable. It is also requested that this Rule 116 Amendment be entered, since it limits any issues for purposes of appeal by removing the 35 U.S.C. Section 112 issue per the suggestion of the Examiner.

The Office Action rejected Claim 8 over a combination of the *Bradwell, et al.* U.S. Patent No. 4,889,815 in view of *Minoru, et al.* Japanese published application 07-035752 in view of the *Hasegawa* Japanese publication 06-265554.

In the measurement of a C-reactive protein (CRP) of the present invention, the whole blood sample is lysed so that the erythrocyte is destroyed and becomes a transparent red color 101. Reference can be made to the attached Figure A wherein the (CRP) antigen 102 and the insoluble carriers 103 in the lysed whole blood are agglutinated by an antigen-antibody reaction. Here, Y 104 is a (CRP) antigen which specifically reacts with the antigen 102. The portion 105 is the agglutinate clot formed by the agglutination. The present invention utilized light in a wavelength range that does not have absorption of hemoglobin (Hb) and this light is irradiated on the clots 105 and the absorbance is measured. As can be seen by the chart in Figure A, the CRP concentration of the lysed whole blood, e.g., CRP concentration plasma (abscissa) can be attained by a calibration curve. Reference can be made, for example, to our Example 6 in our specification. In addition, the hematocrit value can be simultaneously obtained as set forth in Example 7 of our invention. This resulting hematocrit value can be substituted into a correction calculation formula to obtain a hematocrit corrected CRP concentration. Additionally, as can be seen in the attached Figure A, the larger the CRP concentration is, the greater the rate of the

agglutination. Additionally, the hematocrit value is a volume ratio of erythrocyte into the whole blood and is represented by a percentage.

Thus, the present invention teaches an immunoassay method that combines a blood cell measuring technique, namely a blood cell counter with which the hematocrit value can be counted with a measuring technique for treating CRP direct with whole blood (see page 9, lines 14-15 of the present invention).

Claim 8, as previously amended, specifically calls for:

> means for measuring the resulting agglutination mixture for a change in it's absorbance by irradiation with a light of a wavelength free from absorption by both hemoglobin and hemolysis reagent.

Thus, applicants have utilized their statutory rights under the sixth paragraph of 35 U.S.C. Section 112 in defining an element of the present invention. As noted in the case of *In re Iwahashi*, 888 F.2d 1370, 12 U.S.P.Q.2d 1908 (C.A.F.C. 1989), on page 1912:

> The claim is therefore subject to the limitation stated in 35 U.S.C. § 112 Para. 6 that each means-plus-function definition "shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof."[1]
>
> 1 ...Section 112 Para. 6 cannot be ignored when a claim is before the PTO any more than when it is before the courts in an issued patent.

The Office Action acknowledged on page 4 that *Bradwell, et al.* failed to irradiate and measure the reaction product at a wavelength range that is substantially free from absorption by both hemolysis and hemolysis reagent, i.e., 800 nm. As noted above, the means claim element at issue was amended to call for a wavelength range that is free from absorption. Since the *Bradwell, et al.* reference fails to provide any such teaching, the burden of finding such a

teaching to meet the standards of 35 U.S.C. Section 103 rests upon the *Minoru, et al.* Japanese publication 07-035752 and the *Hasegawa, et al.* Japanese publication 06-265554.

The *Minoru, et al.* reference adds purified water to a whole blood sample and heats it for 20 minutes, wherein a monoclonal antibody mixture is added to a latex suspension and heated for another 20 minutes to cause a selective agglutination reaction of latex. A sample with a known Hb AL_c value is used as a standard for performing a similar agglutination reaction in order to be able to determine the percentage of AL_c in an unknown sample. Thus, there is certainly no teaching in the *Minoru, et al.* reference that suggests a solution to the deficiency in the *Bradwell, et al.* reference.

The *Hasegawa, et al.* reference discloses both a method and equipment for analyzing a biochemical component of blood and suggests that in the case of a whole blood, a decision can be made by the equipment as to whether the measuring items are applicable to the whole blood. This reference, however, does not define an irradiation at an wavelength range that is free from absorption by both hemolysis and hemolysis reagent.

Thus, it is clear that both of these secondary references fail to teach the features of the present invention as set forth in Claim 8 wherein the measuring wavelength will be free from absorption of hemolysis and hemolysis reagent, e.g., in the range of 800 nm.

The Office Action appears to set forth, in the last paragraph of page 5, a contention that such a suggestion can be found in *Bradwell* simply because a spectrometer can take measurements at or near an infrared level. This justification is a hindsight approach to fill a gap that exists in the combined teaching of the three cited references. The Office Action has already acknowledged that *Bradwell, et al.* does not provide any such teaching.

Applicants respectfully traverse this interpretation of the *Bradwell, et al.* reference.

Reference can be made with Figure 2 of the *Bradwell, et al.* reference for a comparison with Figure 5 of the present invention. As can be seen, the Bradwell, et al. reference only discloses a wavelength range from approximately 400 to 600 nm. As can be seen in both of the charts of Figures 2 and 5, the wavelength range centering around 400 nm shows absorption of radiation by proteins other than hemoglobin, while a range of approximately 500 to 600 nm shows absorption by hemoglobin. As can be readily determined, *Bradwell, et al.* specifically selects a wavelenth of about 480 nm to show a low absorption of hemoglobin. There is no teaching of considering a wavelength above 600 nm which is proposed and suggested in our present invention and shown on Figure 5 of our present disclosure. Additionally, the *Bradwell, et al.* disclosure is directed to a high degree of scattering and measures the light at a 90° position as shown in Figures 4, 5, 6, and 7. It should also be noted in Column 2, Lines 7-11, that the lysed red cells are particularly prepared so that their fragments become particles of a size which does not scatter light in wavelengths between 460 and 510 nm. This teaching is further reinforced on Column 3, Lines 1-15, wherein it is also pointed out that a high intensity light emitting diode at 480 nm could be used and thereby remove the necessity for filters.

In fact, the alternative embodiments of Figures 1, 6, and 7 only disclose an on-axis detector that is used to time the duration of the light flash to particularly compensate for the absorption of hemoglobin.

In summary, it is quite clear that *Bradwell, et al.* teaches 480 nm wavelength and acknowledges that absorption by hemoglobin will occur and thereby compensates through a circuit which governs the duration of the light flash.

A person of ordinary skill in this field would certainly recognize that there is no teaching at any place in the embodiment of *Bradwell, et al.* that would suggest selecting a wavelength in

the near infrared 800 nm range. Additionally, *Bradwell, et al.* specifically teaches the measurement of a scattering property and does not rely upon a measurement of absorption to determine the formation of an antigen-antibody complex or the amount of a protein in a sample.

The Federal Court of Appeals has provided guidelines in which to address rejections that comprise three separate references with a failure of any of the references, alone or in combination, to provide a teaching that addresses the advantages of the present invention, particularly where the deficiency of the three references are attempted to be compensated by allegedly what would be obvious to a person of ordinary skill in this field.

See *Al-Site Corp. v. VSI International*, 174 F.3d 1308 (Fed. Cir. 1999) at page 1324:

> VSI is unable, however, to point to any specific teaching or suggestion for making this combination. VSI instead relies on what it presumes is the level of knowledge of one of ordinary skill in the art at the time of the invention to supply the missing suggestion to combine. In the first place, the level of skill in the art is a prism or lens through which a judge or jury views the prior art and the claimed invention. This reference point prevents these deciders from using their own insight or, worse yet, hindsight, to gauge obviousness. Rarely, however, will the skill in the art component operate to supply missing knowledge or prior art to reach an obviousness judgment. See *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 312-13 (Fed. Cir. 1983) ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher."). Skill in the art does not act as a bridge over gaps in substantive presentation of an obviousness case, but instead supplies the primary guarantee of objectivity in the process. See *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718, 21 U.S.P.Q.2d 1053, 1057 (Fed. Cir. 1991).

In summary, the present rejection of Claim 8 is not in compliance with the directions of the MPEP Section 2181 for "means for" claim elements, and the application of an obviousness rejection under 35 U.S.C. Section 103 fails to comply with the directions of the Federal Court of Appeals, as noted above.

It is respectfully requested that a reconsideration of this rejection be undertaken, and that the case be passed to allowance.

The *Bradwell, et al.* reference relates to a nephelometric method for determination of an antigen or antibody content in whole blood which uses wavelengths in a range subject to hemoglobin absorption (460 – 530 nm). On the other hand, wavelengths in a range free of hemoglobin absorption (for example, 800 nm) are used in the present invention. *Bradwell, et al.* cannot determine the exact values including absorbance and its change.

The *Minoru, et al.* reference provides a method for immunological assay for agglutination. A sample of whole blood is lysed with water or surfactants, and there are no descriptions nor suggestions for the use of saponin as a hemolytic agent. The hemoglobin in blood cells are determined in *Minoru, et al.*, while Claim 8 of the present invention determines CRP, etc. of the plasma components in the lysed whole blood. In addition, *Minoru, et al.* makes no corrections for a hematocrit percent of the results of the determination.

The *Hasegawa, et al.* reference relates to a method and equipment for analyzing a biochemical component of blood, in which a sample may be whole blood or serum. It does not clearly mention, however, hemolyzing the whole blood.

If the Examiner believes a telephone interview will help further the prosecution of this case, she is respectfully requested to contact the undersigned attorney at the listed telephone number.

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to the Assistant Commissioner for Patents, Box AF, Washington, D.C. 20231 on January 22, 2002.

By: Marc Fregoso

Marc Fregoso

Signature

Date: January 22, 2002

Respectfully submitted,

PRICE AND GESS

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Claim 9 has been amended as follows:

9. (Thrice Amended) An immunoassay method of quantifying a predetermined antigen in a sample of whole blood, comprising the steps of:

providing a sample of the whole blood;

adding a hemolysis reagent [and a latex reagent directly] to the sample of the whole blood [and hemolysing the whole blood sample with the hemolysis reagent] to hemolyse the blood corpuscles;

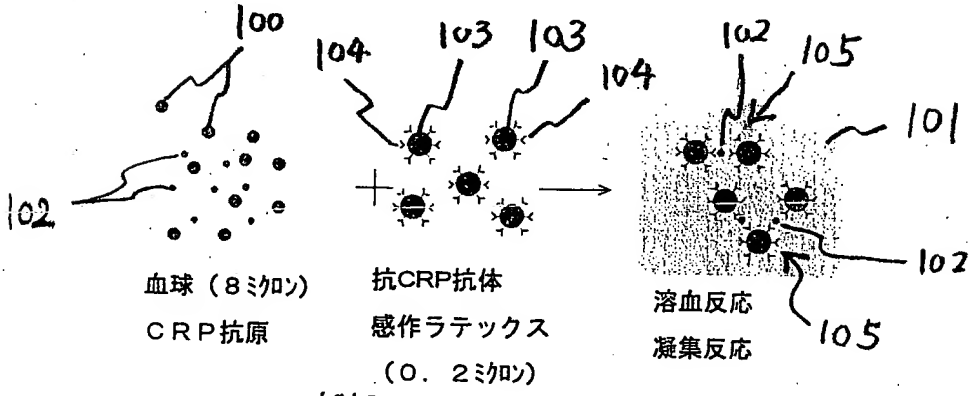
[reacting] adding a latex reagent directly to the hemolysed whole blood sample to react the hemolysed sample in an agglutination reaction to form a reaction product wherein a predetermined antigen in the hemolysed whole blood sample specifically reacts with an antibody immobilized onto an insoluble carrier to provide the reaction product;

irradiating the reaction product in the sample with radiation which includes a wavelength range which is substantially free from absorption by both hemoglobin and the hemolysis reagent; and

measuring only in the wavelength range which is substantially free from absorption by both hemoglobin and the hemolysis reagent, an absorbance of the incident radiation by the reaction product to determine the quantity of antigens in the sample.

ＣＲＰ測定原理

ラテックス免疫比濁法（全血）



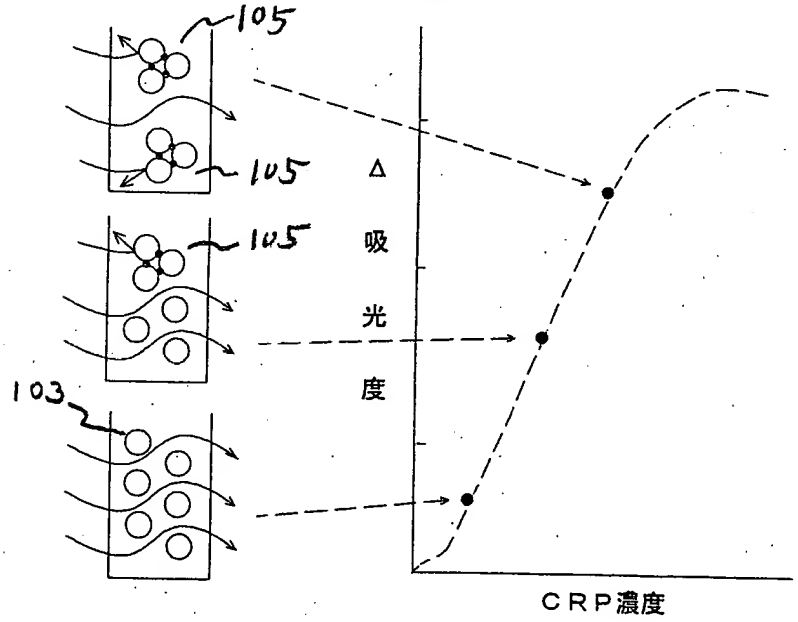


FIG. A